



Hezzell, M. (2018). Pathology and prognosis of canine myxomatous mitral valve disease. *In Practice*, 40(Suppl 1), 3-6.  
<https://doi.org/10.1136/inp.k594>

Peer reviewed version

License (if available):  
CC BY-NC-ND

Link to published version (if available):  
[10.1136/inp.k594](https://doi.org/10.1136/inp.k594)

[Link to publication record in Explore Bristol Research](#)  
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via BMJ Publishing at [http://inpractice.bmj.com/content/40/Suppl\\_1/3](http://inpractice.bmj.com/content/40/Suppl_1/3) . Please refer to any applicable terms of use of the publisher.

## University of Bristol - Explore Bristol Research

### General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:  
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

## **Myxomatous Mitral Valve Disease – an Introduction**

**Melanie Hezzell** graduated from the University of Cambridge in 1997 and worked in mixed and small animal practice for 10 years, during which time she gained the RCVS Certificates and Veterinary Diagnostic Imaging and Veterinary Cardiology. In 2007 she undertook a rotating small animal internship at the RVC, followed by a PhD in the identification of prognostic indicators in myxomatous mitral valve disease at the same institution. She then embarked upon a residency at the University of Pennsylvania, gaining her Diploma in Veterinary Cardiology in 2016. Since then she has been a Senior Lecturer in Cardiology at the University of Bristol. She is interested in all aspects of cardiology, but particularly in myxomatous mitral valve disease and the clinical usefulness of biomarkers.

Myxomatous mitral valve disease is common in small breed dogs. However, the natural history of the disease is variable, with some dogs experiencing rapid progression to congestive heart failure and cardiac-related death, while other dogs have disease that never progresses to produce clinical signs. Treatment is recommended according to the stage of disease progression, so understanding how to make this assessment is important. This article reviews the pathology and natural history of myxomatous mitral valve disease, and provides details of the most commonly used disease staging system.

### **Background**

Myxomatous mitral valve disease (MMVD), also known as degenerative mitral valve disease, chronic valvular disease and endocardiosis, is the most common acquired cardiac disease in dogs, accounting for 75 to 80% of clinical cases. Small- and medium-sized dogs (less than 20 kg bodyweight) are primarily affected, with certain breeds being overrepresented, especially the Cavalier King Charles Spaniel (CKCS). MMVD is frequently detected at a younger age in the CKCS compared with other breeds. Over half of CKCS are affected by 5 years of age and almost all CKCS are affected by the time they are 10 years old. Other predisposed breeds include the dachshund, poodle, Chihuahua and cocker spaniel.

Detection of the disease is straightforward and requires no special equipment, as it can be achieved based on detecting a characteristic left apical systolic murmur on auscultation. Ideally, the diagnosis should be confirmed with echocardiography, but if a characteristic murmur is detected in a middle-aged or older dog of less than 20 kg body weight it is reasonable to assume that MMVD is the cause, should echocardiography not be available.

### **Aetiology**

Despite being so common, the cause of MMVD remains unclear, although it does appear to be inherited. In CKCS, MMVD is believed to be a polygenic threshold trait, with threshold levels being influenced by sex. However, although two genetic loci associated with MMVD in CKCS have been identified, the precise genes involved and their function have yet to be determined. It has been suggested that inherited connective tissue disorders might predispose dogs to develop MMVD, as is the case in human patients, especially as bronchomalacia and tracheal collapse are common in the breeds predisposed to MMVD.

## Pathology

In MMVD the valve apparatus (comprising the valve leaflets, chordae tendineae and valve annulus) undergoes progressive connective tissue weakening due to abnormal collagen organisation and glycosaminoglycan (GAG) accumulation, a process known as myxomatous degeneration. Grossly, this process results in the formation of nodules in the region of valve apposition that, with disease progression, increase in size and eventually coalesce to form plaque-like lesions (Figure 1A). The chordae tendineae are also affected by the process of myxomatous degeneration, which may eventually lead to their rupture (Figure 1B). Although the process of myxomatous degeneration has been well described, the underlying mechanisms of its development and progression remain incompletely understood: this is an area of active research interest.

The resultant instability of the valve leaflets causes them to prolapse, or balloon, into the atrium during ventricular systole. The deformation of the valve leaflets by the process of GAG accumulation prevents complete apposition during systole and so resulting in regurgitation of blood from the ventricle into the atrium. Fibrous plaques may develop in regions of atrial endocardium traumatized by the high-velocity jet of mitral regurgitation (jet lesions). The mitral valve can be affected either alone or in combination with other heart valves, most commonly the tricuspid valve, although the aortic and pulmonic valves may also be involved.

## Pathophysiology of Mitral Regurgitation

Typically, the process of myxomatous degeneration is slow, developing over months to years. However, it is easier to illustrate the pathophysiology by considering the acute development of mitral regurgitation (MR).

The total stroke volume (TSV) is the volume of blood ejected from the ventricle during systole, representing the difference between the ventricular end-diastolic (maximum) and end-systolic (minimum) volumes (the fraction of the end-diastolic volume that is ejected from the ventricle, or ejection fraction (EF) is normally around 50-65%). The forward stroke volume (FSV) is the volume of blood ejected into the aorta. If we imagine a healthy dog with a forward stroke volume of 100mL (in reality this volume would be much smaller), the mitral valve leaflets coapt fully, preventing any regurgitation of blood into the atrium; therefore FSV and TSV both equal 100mL in this case (Figure 2).

If the mitral valve develops an acute leak in our imaginary patient allowing 5mL of blood to enter the atrium rather than being ejected into the aorta, the TSV remains 100mL, but the FSV decreases to 95mL; the 5mL that leaks into the atrium is termed the regurgitant stroke volume (RSV) (Figure 3a).

Cardiac output (CO) is the volume of blood ejected into the aorta per minute and equals FSV x heart rate. The decrease in FSV will initially be detected by the baroreceptors in the aorta, which respond by increasing sympathetic drive to the sinus node and so compensate for the decrease in FSV in the short term by increasing heart rate, thereby normalizing CO.

The decrease in FSV causes a decrease in systemic blood pressure and hence a decrease in the concentration of sodium chloride in the distal tubule of the kidney. This decrease in salt concentration is sensed in the kidney by the macula densa, which signals to the cells of the juxtaglomerular apparatus to release renin, triggering the renin-angiotensin-aldosterone (RAAS)

cascade, responsible for vasoconstriction and retention of salt and water, thereby normalizing blood volume and returning FSV to 100mL. As a result, end-diastolic volume increases to 205 mL and TSV increases to 105mL (Figure 3b). End-diastolic volume therefore increases by 5mL, while end-systolic volume remains unchanged, resulting in a slight increase in EF (Figure 3c); systolic function therefore appears hyperdynamic on echocardiography. In response to this increase in end-diastolic volume, the ventricular myocardium enlarges by eccentric hypertrophy, in which additional cardiomyocytes are added in series. As a result, the ventricle dilates and takes on a more globoid appearance (Figure 4). Similarly, the atrium dilates to accommodate the 5mL of RSV. Left atrial and ventricular enlargement allows for normalization of chamber pressures, thereby avoiding the development of secondary increases in pulmonary venous pressures that would eventually result in pulmonary oedema.

If the RSV remains modest, these compensatory mechanisms allow for normalization of cardiac output without a significant decrease in cardiac performance or increase in intracardiac pressures. Although the patient has heart disease, it would not demonstrate any clinical signs at this stage; in these cases a murmur is often detected at the time of routine vaccination in an otherwise healthy dog. Unfortunately, the process of myxomatous degeneration is often progressive, leading to worsening MR over time. Additionally, the development of prolapse and regurgitation increase valvular shear stress, which is likely to result in further damage to the leaflets, while eccentric ventricular hypertrophy causes dilation of the valve annulus, further impairing coaptation. As a result, MR can bring about worsening MR. The processes of RAAS activation and atrial and ventricular dilation, which are initially compensatory, eventually become deleterious. The left atrium is no longer able to compensate for the increased RSV by dilation, resulting in increased pressures in the atrium, and then the pulmonary vein. Increased pulmonary venous pressures decrease reabsorption of fluid from the pulmonary interstitium in the distal capillaries, resulting in the accumulation of interstitial oedema and hence congestive heart failure. Although systolic function is not directly affected by MMVD (being a disease of the valve rather than the myocardium), in severe cases the myocardium will eventually start to fail.

### ACVIM Staging System

In 2009 the American College of Veterinary Internal Medicine (ACVIM) published a consensus statement, outlining treatment recommendations for dogs with MMVD (an updated consensus statement is planned to be published in the near future). Separate treatment recommendations were made according to the stage of disease progression; this scheme of staging of MMVD has been widely adopted by cardiologists.

Dogs are assigned to 4 main categories, which are ascribed the letters A-D (Table 1). It is important to note that progress through these disease stages is one-way; once a patient progresses to Stage C, for example, it does not return to Stage B once it has stabilised clinically after initiation of therapy. Further numerical subcategorization is also used, the most clinically important being the subcategorization of stage B into stages B1 and B2.

### Clinical Disease Progression and Outcome

The pathophysiology of disease progression in a theoretical patient is described above. However, information about the progression of MMVD in real patients is, of course, much more clinically relevant. Fortunately, a number of longitudinal studies have been performed to elucidate this.

Importantly, not all cases of MMVD are progressive and less than 50% of dogs with MMVD will die as a result of their disease. Observational studies in which dogs with MMVD underwent serial examinations have shown that a number of measurable factors increase over time in dogs that subsequently develop congestive heart failure and die as a result of their heart disease. These include radiographic heart size (assessed using the vertebral heart sum (VHS)), echocardiographic measurements of left atrial and ventricular size and circulating biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI). Furthermore, the rates of change in these variables accelerates with disease progression. If dogs with Stage B1 disease (a murmur but no evidence of cardiomegaly) are monitored over time, many will prove to have stable, non-progressive disease and will never develop cardiomegaly. However, once progression to Stage B2 occurs, the risk of subsequently developing congestive heart failure is significantly increased (although not inevitable).

It should also be remembered that these disease stages represent a continuum; dogs with mild cardiomegaly have a significantly lower risk of congestive heart failure than those with severe left atrial enlargement although both would be assigned to Stage B2. The differentiation between Stage B1 and Stage B2 is clearly important for estimates of prognosis. Following the publication of the EPIC trial it is also important for therapeutic decision making ([www.epictrial.com](http://www.epictrial.com)).

#### *Risk Factors for Disease Progression and Mortality*

A number of studies have investigated risk factors for disease progression and mortality. Risk factors for disease progression in dogs with Stage B MMVD include radiographic evidence of cardiomegaly (increased VHS), left ventricular dilation, increased circulating NT-proBNP and increased early diastolic ventricular filling wave (E wave) velocity (which provides an estimate of left atrial filling pressure). Risk factors for mortality include left atrial enlargement, left ventricular dilation, increased E wave velocity, increased circulating NT-proBNP, increased circulating cTnI, and increased heart rate.

#### **Non-echocardiographic risk factors**

These risk factors include variables that can easily be assessed in primary practice (such as increased VHS, increased heart rate and circulating NT-proBNP and cTnI). Unfortunately, all of these prognostic indicators have limitations.

VHS is a measure of global heart size, and increases are not specific for left-sided cardiomegaly. The VHS is also not a sensitive way to detect increases in left atrial size; the left atrium contributes little to the VHS measurements due to its caudodorsal position on a lateral radiograph, although this does not preclude a radiographic assessment of left atrial enlargement in these cases (Figure 5). Furthermore, in certain breeds, dogs with echocardiographically normal hearts can have a VHS that exceeds the upper limit of the standard reference interval, resulting in Stage B1 dogs being misclassified as Stage B2. Such breeds include the CKCS, dachshund, pug, Pomeranian, English bulldog, Boston terrier, boxer and Labrador retriever; given that CKCS and dachshund are particularly overrepresented, this has clear clinical importance in MMVD.

Increases in heart rate are also a non-specific change, as this may be associated with any physiological state that leads to increased sympathetic tone (e.g. stress, anxiety, pain, etc.). NT-proBNP is the inactive fragment released during production of BNP, a neurohormone with actions of natriuresis, diuresis and vasodilation which is released in response to myocardial stretch (i.e. increased ventricular blood volume).

MMVD is characterised by cardiac volume overload; as a result, circulating NT-proBNP concentrations start to increase relatively early in the disease process and continue to increase with disease progression. Circulating NT-proBNP measurements are subject to significant biological variability, which can result in fluctuations in serial measurements, even in healthy animals. Changes in plasma NT-proBNP measurements of up to 70-80% can fall within the expected range of variability, and should not be interpreted as indicative of disease progression. However, if plasma NT-proBNP concentration in an individual dog increases by more than 100-110%, disease progression is more likely; in one study, a doubling of circulating NT-proBNP over a 13-month period was associated with an increased risk of cardiac mortality. Furthermore, in certain breeds (such as Labrador retrievers), animals with echocardiographically normal hearts may have plasma NT-proBNP concentrations above the standard laboratory reference interval, which may result in an unwarranted increased in clinical suspicion of cardiac disease. Nevertheless, so long as these factors are considered, serial monitoring of plasma NT-proBNP might be a useful way to monitor dogs in which access to echocardiography is limited.

Cardiac troponin I is an intracellular molecule that forms part of the contractile apparatus of the myocyte – its release into the circulation therefore indicates cellular disruption and it is used as a marker of cardiac damage. As MMVD is not primarily a myocardial disease, cTnI is generally either within the laboratory reference interval or only mildly increased until the latter stages of the disease. One study showed that circulating cTnI concentrations in dogs that died due to their heart disease only diverge from those that died due to non-cardiac causes in the last 6 months of life. The utility of this marker for staging the disease and monitoring progression is therefore limited.

### **Echocardiographic risk factors**

Although MMVD can be diagnosed with reasonable confidence on detection of a left apical systolic heart murmur in a middle-aged or older, small- to medium-sized dog, echocardiography is helpful to confirm the diagnosis and exclude any other congenital or acquired cardiac abnormalities, as discussed elsewhere in this supplement. Echocardiography is also important to accurately stage the disease (in particular to differentiate stage B1 from stage B2 dogs) and to estimate prognosis. The most established echocardiographic prognostic indicators include left atrial and ventricular enlargement and increased E wave velocity, although other risk factors, such as severity of valve prolapse, have also been identified.

Standard echocardiographic measurements of left atrial and ventricular dimensions are fraught with the potential for inaccuracy, as they involve measurements of a non-geometric three-dimensional structure on a two-dimensional image. If the incorrect image plane is chosen (for example, too apical in the ventricle or an oblique rather than a truly transverse plane) these dimensions can be significantly under- or over-estimated, resulting in potential misclassification. Nevertheless, with training and experience, these measurements can be made with good repeatability and reproducibility; echocardiographic staging should be performed by experienced operators.

### **Summary**

The owners of dogs diagnosed with cardiac disease are often understandably concerned about what the future might hold. Understanding the pathophysiology and natural history of this common cardiac disease is invaluable in counselling owners; importantly, in many dogs the disease is relatively benign. This knowledge is also key to understanding why the risk factors for progression and mortality are important. Accurate disease staging is imperative to ensure that appropriate treatment recommendations are made.

Figure 1: Postmortem specimens from a dog with myxomatous mitral valve disease. (a) Typical coalescing nodular lesions, especially along the leaflet edges, (b) two ruptured chordae tendineae (black arrows). Pictures: Ross Harley.

(a)



(b)

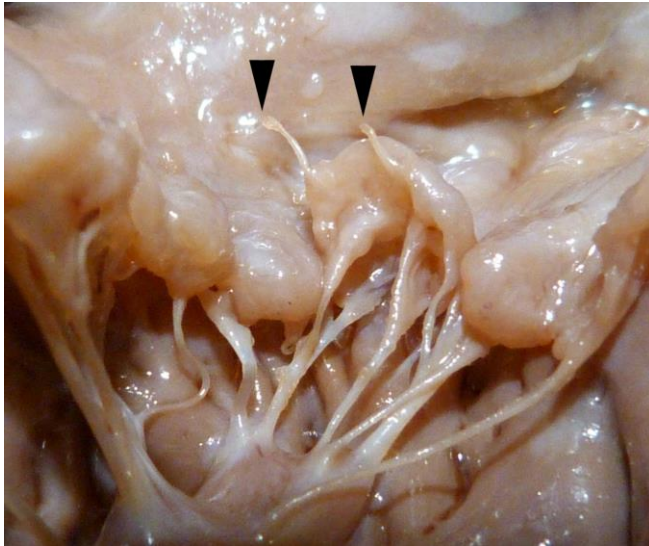


Figure 2: Illustrative cardiac volumes in a healthy dog in the absence of mitral regurgitation and (a) end diastole and (b) end systole.

EDV End-diastolic volume, ESV End-systolic volume, FSV Forward stroke volume. Ejection fraction = 50% ( $[(EDV - ESV) / EDV] \times 100$ ). Note: Actual cardiac volumes would be significantly smaller in most breeds of dog.

Figure 3: Illustration of the pathophysiological effects of (a) the development of acute mitral regurgitation, (b) an increase in circulating volume secondary to renin-angiotensin-aldosterone system activation and (c) the resultant increase in ejection fraction.

EDV End-diastolic volume, ESV End-systolic volume, RSV Regurgitant stroke volume, TSV Total stroke volume, FSV Forward stroke volume. Ejection fraction = 51.2% ( $[(EDV - ESV) / EDV] \times 100$ ). Note: Actual cardiac volumes would be significantly smaller in most breeds of dog.

Figure 4: Three-dimensional echocardiographic images of the left ventricle from a healthy dog (left) and a dog with ventricular remodelling secondary to progressive myxomatous mitral valve disease (right), demonstrating the changes associated with volume overload.

Reproduced with permission from: Ljungvall and others (2011).



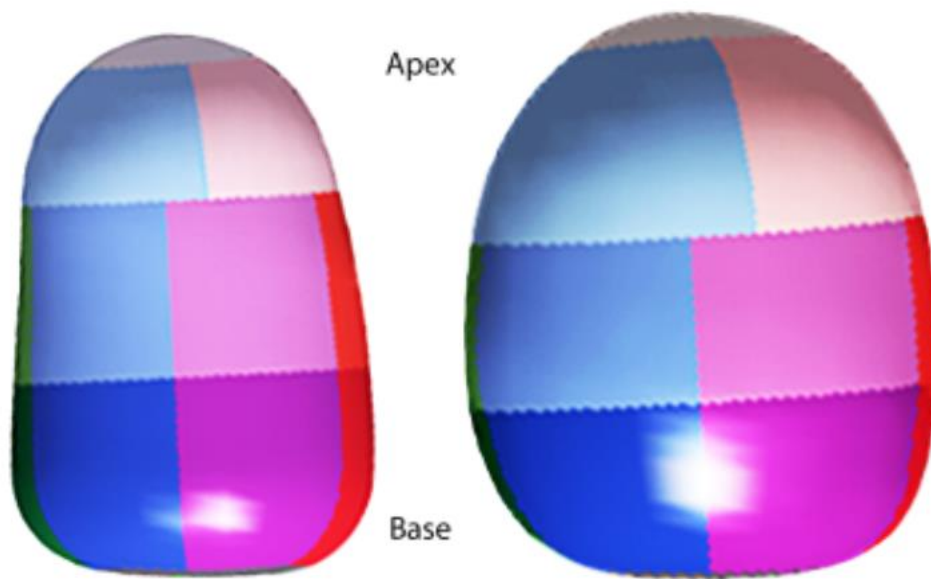


Figure 5: Lateral radiograph of the thorax, showing the measurements used to calculate the vertebral heart sum (VHS) in blue and the outline of the left atrium in red.

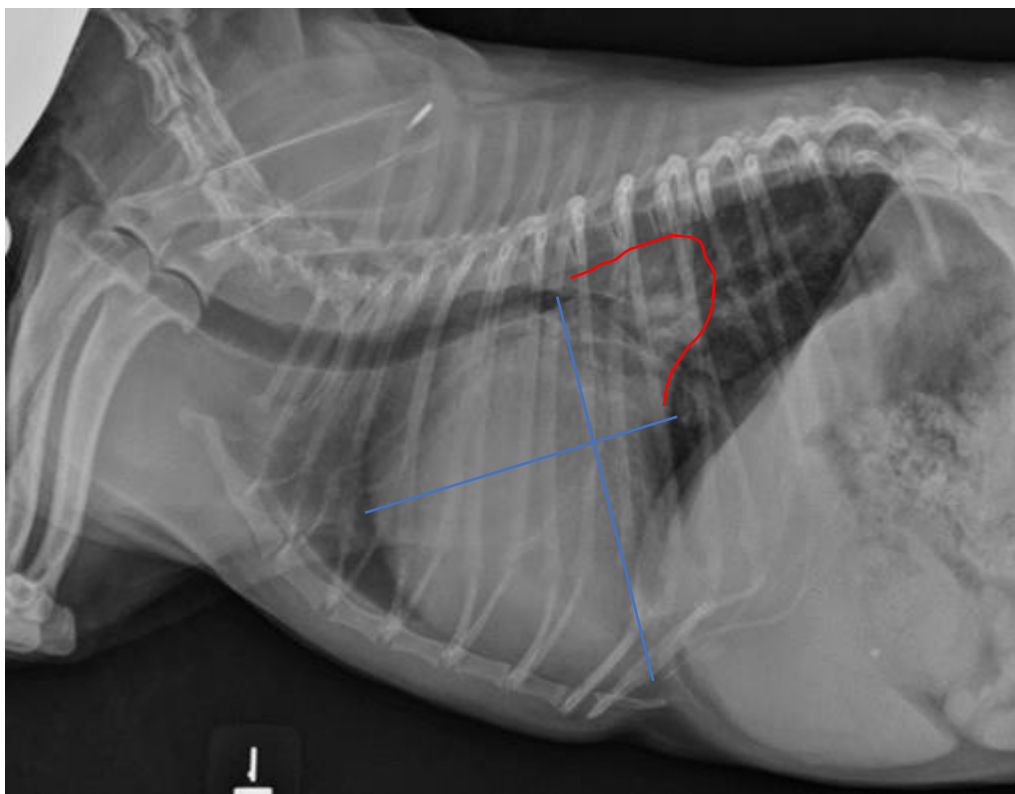


Table 1: The American College of Veterinary Internal Medicine's classification scheme for myxomatous mitral valve disease in dogs. Adapted from Atkins, Bonagura et al (2009) "Guidelines for the diagnosis and treatment of canine chronic valvular heart disease" Journal of Veterinary Internal Medicine 23:1142-1150.

ACVIM Stage	Description		
Stage A	Patients with no current evidence of heart disease that are at high risk for future development of disease (e.g. any cavalier King Charles spaniel without a cardiac murmur)		
Stage B	Patients with evidence of structural heart disease (e.g. a left apical systolic heart murmur) but no current or previous evidence of congestive heart failure	Stage B1	Patients that have no radiographic or echocardiographic evidence of cardiac remodelling
		Stage B2	Patients with radiographic or echocardiographic evidence of left-sided heart enlargement
Stage C	Patients with past or current evidence of congestive heart failure (even if clinically stable on therapy)		
Stage D	Patients with end-stage disease with clinical signs of congestive heart failure that are refractory to standard therapy (furosemide, pimobendan, an ACE inhibitor ± spironolactone). Advanced therapeutic strategies are necessary to achieve clinical stabilisation in these patients		

## References

(Buchanan 1977, Kittleson and Kienle 1998, Borgarelli, Savarino et al. 2008, Moonarmart 2008, Atkins, Bonagura et al. 2009, Moonarmart, Boswood et al. 2010, Ljungvall, Hoglund et al. 2011, Borgarelli, Crosara et al. 2012, Hezzell, Boswood et al. 2012, Hezzell, Boswood et al. 2012)

Atkins, C., J. Bonagura, S. Ettinger, P. Fox, S. Gordon, J. Haggstrom, R. Hamlin, B. Keene, V. Luis-Fuentes and R. Stepien (2009). "Guidelines for the diagnosis and treatment of canine chronic valvular heart disease." J Vet Intern Med **23**(6): 1142-1150.

Borgarelli, M., S. Crosara, K. Lamb, P. Savarino, G. La Rosa, A. Tarducci and J. Haggstrom (2012). "Survival characteristics and prognostic variables of dogs with preclinical chronic degenerative mitral valve disease attributable to myxomatous degeneration." J Vet Intern Med **26**(1): 69-75.

Borgarelli, M., P. Savarino, S. Crosara, R. A. Santilli, D. Chiavegato, M. Poggi, C. Bellino, G. La Rosa, R. Zanatta, J. Haggstrom and A. Tarducci (2008). "Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease." J Vet Intern Med **22**(1): 120-128.

Buchanan, J. W. (1977). "Chronic valvular disease (endocardiosis) in dogs." Adv Vet Sci Comp Med **21**: 75-106.

Hezzell, M. J., A. Boswood, Y. M. Chang, W. Moonarmart, K. Souttar and J. Elliott (2012). "The combined prognostic potential of serum high-sensitivity cardiac troponin I and N-terminal pro-B-type natriuretic peptide concentrations in dogs with degenerative mitral valve disease." J Vet Intern Med **26**(2): 302-311.

Hezzell, M. J., A. Boswood, W. Moonarmart and J. Elliott (2012). "Selected echocardiographic variables change more rapidly in dogs that die from myxomatous mitral valve disease." J Vet Cardiol **14**(1): 269-279.

Kittleson, M. D. and R. D. Kienle (1998). Myxomatous atrioventricular valvular degeneration. Small Animal Cardiovascular Medicine. M. D. Kittleson and R. D. Kienle. St. Louis, Mosby: 297-318.

Ljungvall, I., K. Hoglund, C. Carnabuci, A. Tidholm and J. Haggstrom (2011). "Assessment of global and regional left ventricular volume and shape by real-time 3-dimensional echocardiography in dogs with myxomatous mitral valve disease." J Vet Intern Med **25**(5): 1036-1043.

Moonarmart, W., A. Boswood, V. Luis Fuentes, D. Brodbelt, K. Souttar and J. Elliott (2010). "N-terminal pro B-type natriuretic peptide and left ventricular diameter independently predict mortality in dogs with mitral valve disease." J Small Anim Pract **51**(2): 84-96.